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Changes in Ovarian Stromal Function and Associated Symptoms in Premenopausal Women Undergoing Chemotherapy for Breast Cancer

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14. ABSTRACT
The objective of this pilot study was to identify if androgen levels are adversely affected by adjuvant chemotherapy for breast cancer and whether low androgen levels are correlated with the frequency and severity of fatigue, weight gain, psychological symptoms, vasomotor symptoms and libido. A longitudinal, descriptive design was used with questionnaires completed and blood drawn from 20 premenopausal women at 4 time periods: before treatment, mid-treatment, immediate post-treatment and 6 months later. Questionnaires included the Female Sexual Function Index, Greeene Climacteric Scale, Profile of Mood States, Schwartz Fatigue Scale and a menses diary. Data analysis involved descriptive statistics, plots of hormone levels over time, t-tests to examine changes in hormone levels, and correlational analysis to determine relationships between hormone levels and symptoms. Preliminary data indicate that women $\geq$ 40 stopped menstruating, had FSH levels > 40 IU/l and androgen function decreased by at least 35%. Women < 40 retained ovarian function. Sexual function, vasomotor symptoms, vigor and fatigue became progressively worse through treatment. These data provide evidence that chemotherapy impacts androgens.

15. SUBJECT TERMS
Symptom management, clinical oncology, quality of life, androgen levels, breast cancer.

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Introduction
This final report provides the status of the protocol "Changes in Ovarian Stromal Function and Associated Symptoms in Premenopausal Women Undergoing Chemotherapy for Breast Cancer". Preliminary analyses of data have been completed through the end of treatment. We obtained measurements on the last two patients this week. We are entering these final data and will begin final data analyses in September.

Task 1: Work with a collaborative team to develop protocol of pilot study "Changes in Ovarian Stromal Function in Premenopausal Women Receiving Chemotherapy for Breast Cancer" months 1 and 2

Task completed with HSRRB and IRB approval received 4/05.

Task 2: Attend mentoring sessions and educational meetings, months 2 through 24.

Task completed prior to 2006 and 2007 no-cost extensions. I have continued participation in several ongoing educational meetings and mentoring opportunities. My participation this past year includes:

- Work with Dr. Lynn Hartmann and her research team on her Department of Defense Center of Excellence in Breast Cancer grant. I have attend weekly meetings; participated in writing of articles, grant proposals and reports. I continue to work closely with the team of study coordinators and statistical team in the collection, clean-up and analysis of data as well as in management of the budget.

- Attended several educational meetings:
    - Monthly Oncology Nursing Society Meetings
    - Monthly Medical Oncology Society Meetings
    - Department of Defense Era of Hope Meeting

- Work with Dr. Wes Petersen to use Nvivo for the analysis of qualitative data from a study exploring the perceived educational needs of women newly diagnosed with breast cancer.

Task 3: Get approval for pilot study, set up systems to implement study, months 3 - 6

The timeline for the study was delayed. Initial Mayo Clinic IRB approval was obtained November 26, 2002. DOD IRB revisions were made and subsequently approved by Mayo Clinic IRB on 7/29/2003 and 7/6/2004. Responses to recommendations/considerations put forth by the HSRRB minutes of September 22, 2004 were approved by the DOD March 17, 2005 and subsequently by Mayo Clinic IRB March 2005. Questionnaires were duplicated and the mechanisms for blood draws were established during this same time period.

Task 4: Accrue to study, months 7 - 18

Accrual began June 1, 2005. Initial accrual difficulty resulted from eligible women deciding to have chemotherapy at their home institution. We were able to work with our laboratory to facilitate the patient blood draws at their home institution and have them mailed back to Mayo Clinic. However, this approach also proved difficult due to the processing and shipping of the blood. Our next approach was to collaborate with Mayo Clinic Jacksonville to enroll patients.

This past week we collected the final data point for the last two women. Thus, 20 eligible women finished all data points. Women not completing the study included four women became ineligible after study enrollment including three women who had oophorectomies prior to study completion and one woman who was given a luteinizing hormone-releasing hormone agonist. An additional three women did not complete all study components: two did not complete their final questionnaires and blood draws and a third woman was missing lab values for one time point.

Task 5: Data entry and analysis, months 19-24.

Data has been entered into a database as it is received. Preliminary analyses of data has been completed. We are entering the data on the final two women and will begin final data analyses in September.

Task 6: Final analysis and report writing, month 24

Preliminary data analyses has been completed and were presented at the Era of Hope meeting June 2008. Final data analyses will begin September 2008.

Task 7: Strategize follow-up study and program of research based on pilot data, month 24.

Preliminary data suggest that androgens are impacted by chemotherapy. A larger study that documents this finding is warranted. A larger study would also allow the exploration of confounding variables that may influence study outcomes. The current study provides valuable preliminary data for such a grant proposal. However, in the conduction of such a study, the eligibility barrier will need to be addressed. Specifically, many of the women who met study criteria chose to have their treatment closer to home. Preliminary work with our laboratories as to how these tests may be completed in a simplistic manner is needed. We would also need to be actively involved with both our Jacksonville and Scottsdale sites. Both of these sites, compared to the Rochester site, have a greater percentage of patients who are followed through treatment. Any future study needs to include all three of our Mayo Clinic sites as well as to include funding for study coordinators at those sites to identify women, track their progress and meet them for follow-up visits to facilitate data collection.

My work with Dr. Hartmann during this time has been very productive and exciting. My current plan consists of taking the lead on writing one of the risk factor model building papers. I added a quality of life component to the mailed questionnaire in which the woman was asked open-ended questions about how their benign biopsy affected them psychologically and physically. These data are currently being coded. Data will then be entered and analyzed, using demographic, medical and family history variables to identify response trends based on these variables. The results of these data will guide future quality of life inquiries. I am also taking an active role in the line of investigation exploring the significance of breast involution in predicting breast cancer risk. These activities will result in continued mentoring by Dr. Hartmann, the current involvement in preparation of grant proposals and future lead in writing proposals.

Key Accomplishments

- Addressed pre-review considerations included in the HSRRB minutes of September 22, 2004

- Approval by HSRRB March 17, 2005, pending completion of paperwork by Mayo's Institutional Official

- Approval of changes for HSRRB minutes of September 22, 2004 by Mayo Clinic IRB March, 2005

- Approval of a one year no-cost extension April 2005 (to extend research period to July 31, 2006)

- Study opened for accrual June 1, 2005

- Approval of a second one year no-cost extension June 2006 (to extend research period to July 31, 2007

- Accrual of 20 eligible women; 18 completed all data points and 2 have one data point remaining as of August 1, 2007

- Approval of a third one year no-cost extension July 2006 (to extend research period to July 31, 2008)

- Accrual of data on 20 eligible women (three additional women were replaced since August 2007 due to missing key data).

Reportable Outcomes

- Reviewed manuscripts for *JAMA and Archives, Journal of Clinical Oncology, Cancer, Psycho-Oncology, Annals of Internal Medicine* as a means to enhance my knowledge regarding critical writing skills and publications (ongoing)

- Reviewer, National Cancer Institutes, SBIR topics: developing item response theory software for outcomes and behavioral measurement and integrating patient-reported outcomes in clinical oncology practice, 2005, 2006

- Reviewer, Department of Defense, Clinical and Experimental Therapeutics Section, July 2008

- Poster presentation of preliminary data, Era of Hope, June 2008

- Attended a two day Nvivo class to learn this qualitative software package; attended a second advanced Nvivo class to increase skills using this software package (2007)

- Publications in conjunction with

Dr. Lynn Hartmann and colleagues

- **Frost MH**, Slezak JM, Tran NV, Williams CI, Johnson JL, Woods JE, Petty PM, Donohue JH, Grant CS, Sloan JA, Sellers TA, Hartmann LC. Satisfaction after contralateral prophylactic mastectomy: The significance of mastectomy type, reconstructive complications, and body appearance. *Journal of Clinical Oncology*. 2005;23(31):7849-56.

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Dr Jeff Sloan and colleagues

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- Halyard M, Dueck A, **Frost MH**. Integrating quality of life assessments for clinical and research purposes. *Current Problems in Cancer*. 2006;30(6):319-30.

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Other Colleagues

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Conclusions

I have continued to have the opportunity to work with several researchers and their teams as a means to build my knowledge in regards to quality of life research, statistical procedures, team approaches to research, the article review process, manuscript preparation and submission, grant preparation and grant reports. Relationships have been build for ongoing work with these researchers and their teams.

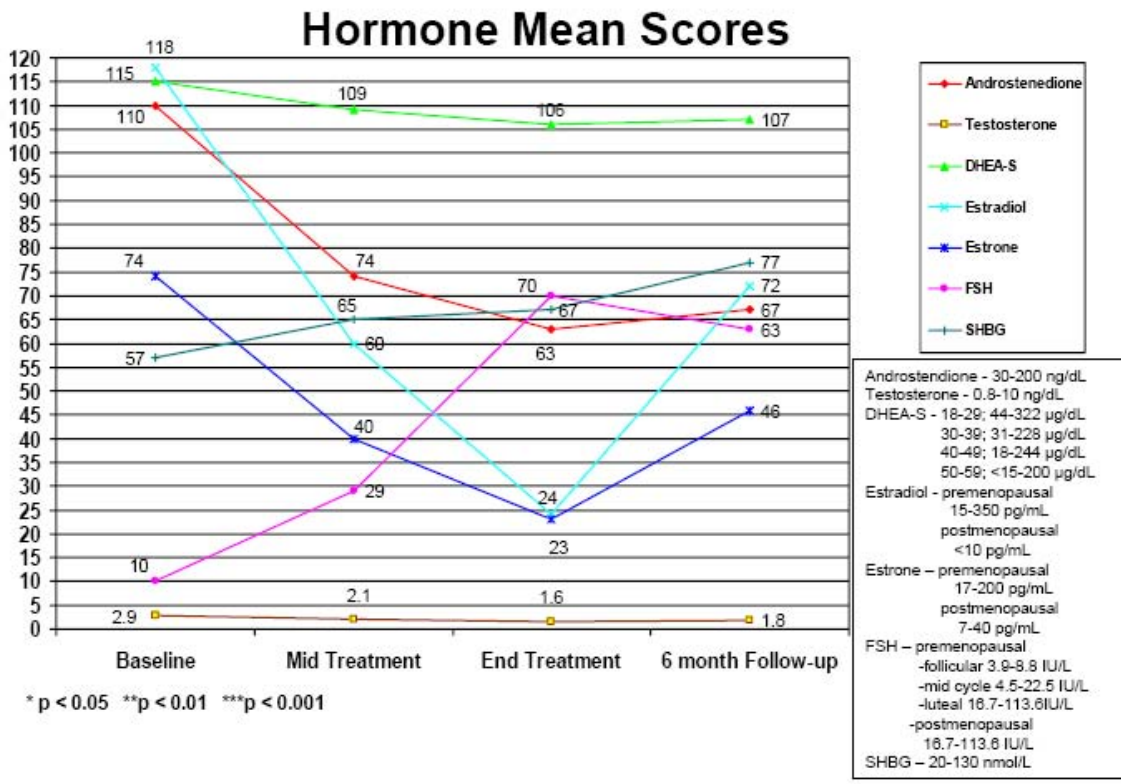
We have enrolled the proposed 20 eligible women for this pilot study who have completed all four data points. We have conducted preliminary data analysis. We are currently entering the last of the data. Final data analysis will begin September 2008, followed by manuscript preparation.

Appendix A: Abstract, Preliminary Data Analysis

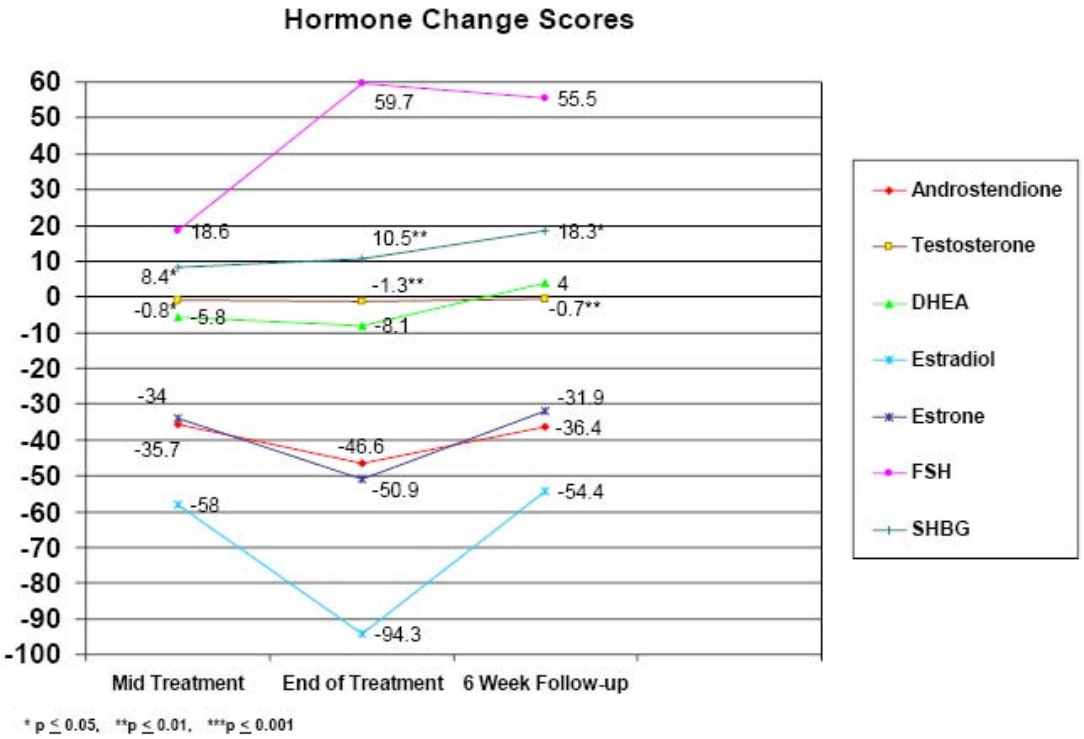
Changes in Ovarian Stromal Function and Associated Symptoms in Premenopausal Women Undergoing Chemotherapy for Breast Cancer

The quality of life of women diagnosed under age 50 can be adversely affected by premature menopause as a result of chemotherapy agents used to treat breast cancer. Menopause-related symptoms are salient management issues for these women and include hot flashes, vaginal dryness, decreased sexual desire, and negative mood swings. Although estrogen levels and follicular function post chemotherapy have been studied, little is known about how or if androgen levels are affected by chemotherapy and whether androgen changes impact symptoms in breast cancer survivors. The objective of this pilot study is to look for evidence of whether androgen levels are adversely affected in premenopausal women as a result of adjuvant chemotherapy for breast cancer and whether low androgen levels are linked to any undesired symptoms. A longitudinal, descriptive design was used. Data, including both subjective and objective measures of menopause- related phenomena, were collected for 20 women who completed blood draws and questionnaires at 4 time periods; baseline (before treatment), mid-treatment, immediate post-treatment and 6 months later. Self report questionnaires included the Female Sexual Function Index, Greene Climacteric Scale, the Profile of Mood States (POMS), the cognitive and physical subscales of the Schwartz Cancer Fatigue Scale (SCFS) and a menses diary. Data analysis included descriptive statistics, specifically, plots of the hormone levels, and change scores over time. Preliminary data are presented from baseline to immediate post treatment. All of the women aged 40 and over did stop menstruating and had an FSH level over 40 IU/L by the end of chemotherapy. Of these women, both estradiol and estrone levels were in the postmenopausal range. For all postmenopausal women, androgen concentrations had decreased by at least 35% from baseline, with most levels decreasing 50%. Androstenedione was more consistently lower than bioavailable testosterone concentrations. The women aged 28 to 39 retained ovarian function as evidenced by estrogen levels in the premenopausal category, low FSH levels and some episodic menstrual activity. Several symptoms became progressively worse through treatment and showed a decline of more than 10 points on a 100 point scale by the end of treatment. These symptoms included all domains of sexual functioning (desire, arousal, lubrication, orgasm, satisfaction and pain), vasomotor symptoms, and vigor and fatigue. These exploratory data provide evidence that androgens are impacted by chemotherapy treatment. This hypothesis should be confirmed in a larger study. Symptoms, such as vasomotor problems, sexual function changes, and fatigue need to be evaluated in patients throughout treatment and interventions begun early in an effort to prevent negative experiences.

Appendix B: Hormone Mean Scores

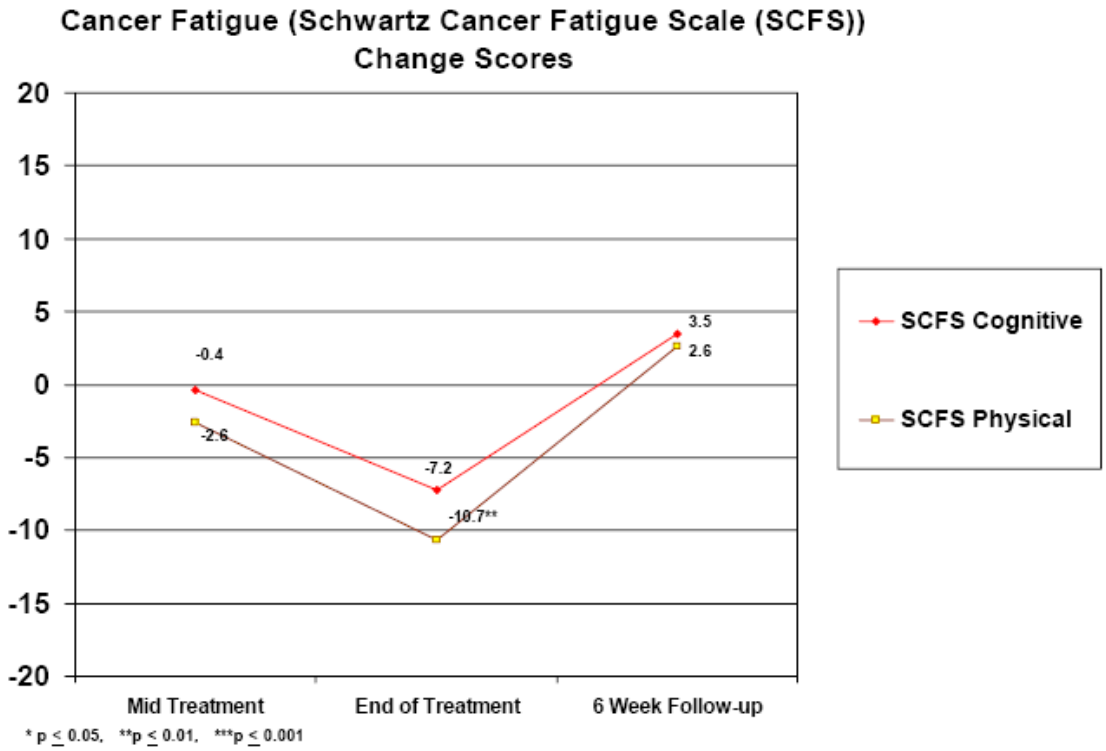


Appendix C: Hormone Change Scores



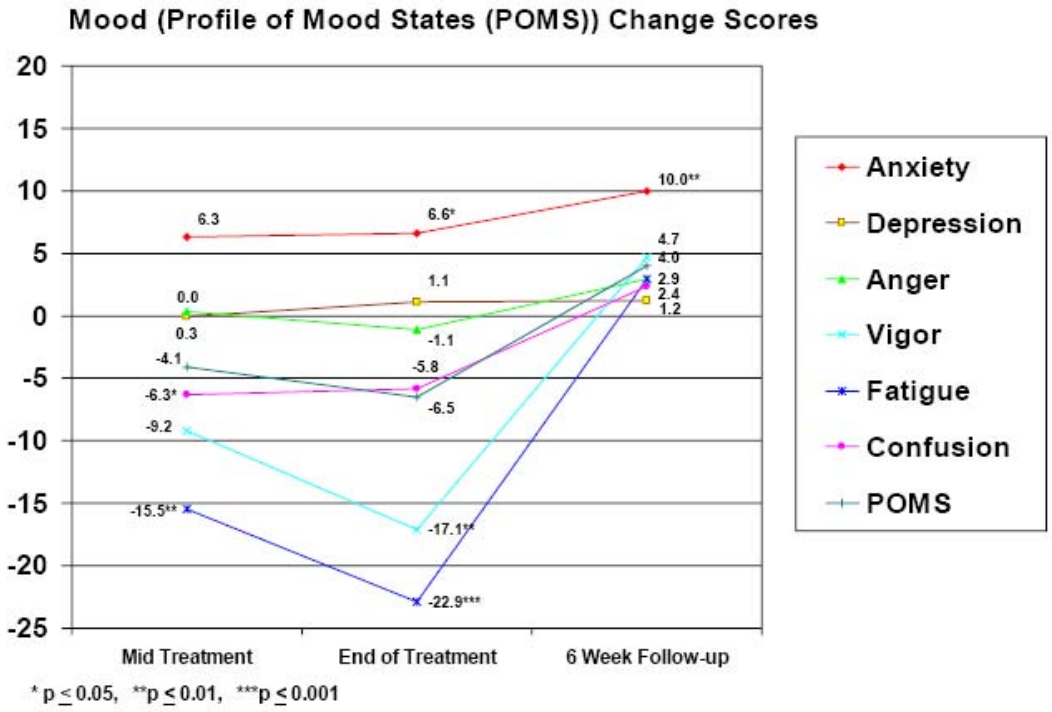
* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

Appendix D: Cancer Fatigue Change Scores



NOTE: SCFS scores transformed to 0-100 scale with high scores representing favorable aspect of concept

Appendix E: Mood Change Scores

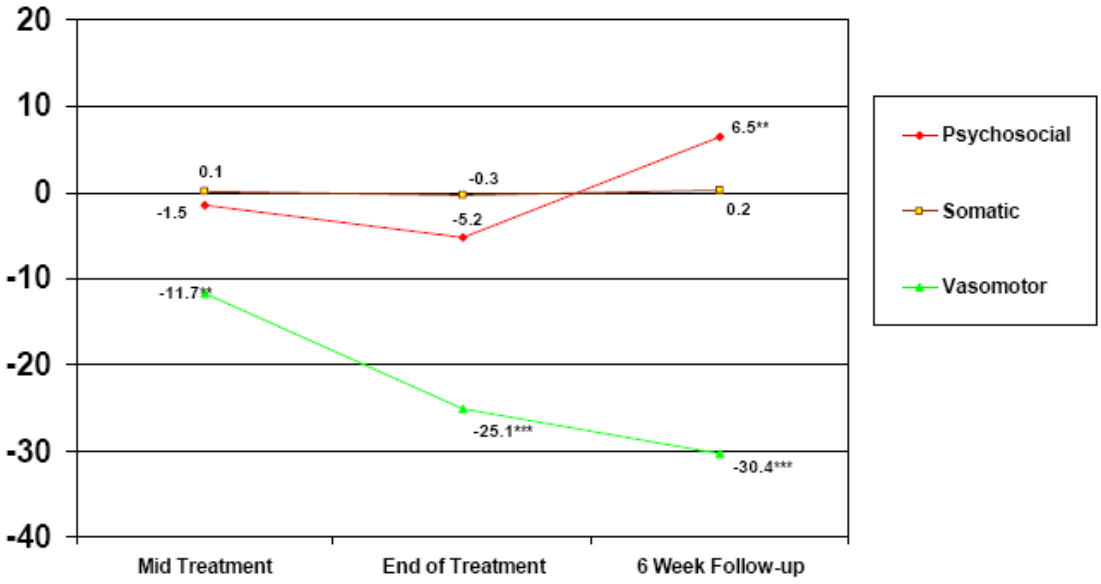


* p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

NOTE: POMS scores transformed to 0-100 scale with high scores representing favorable aspect of concept

Appendix F: Vasomotor Symptoms Change Scores

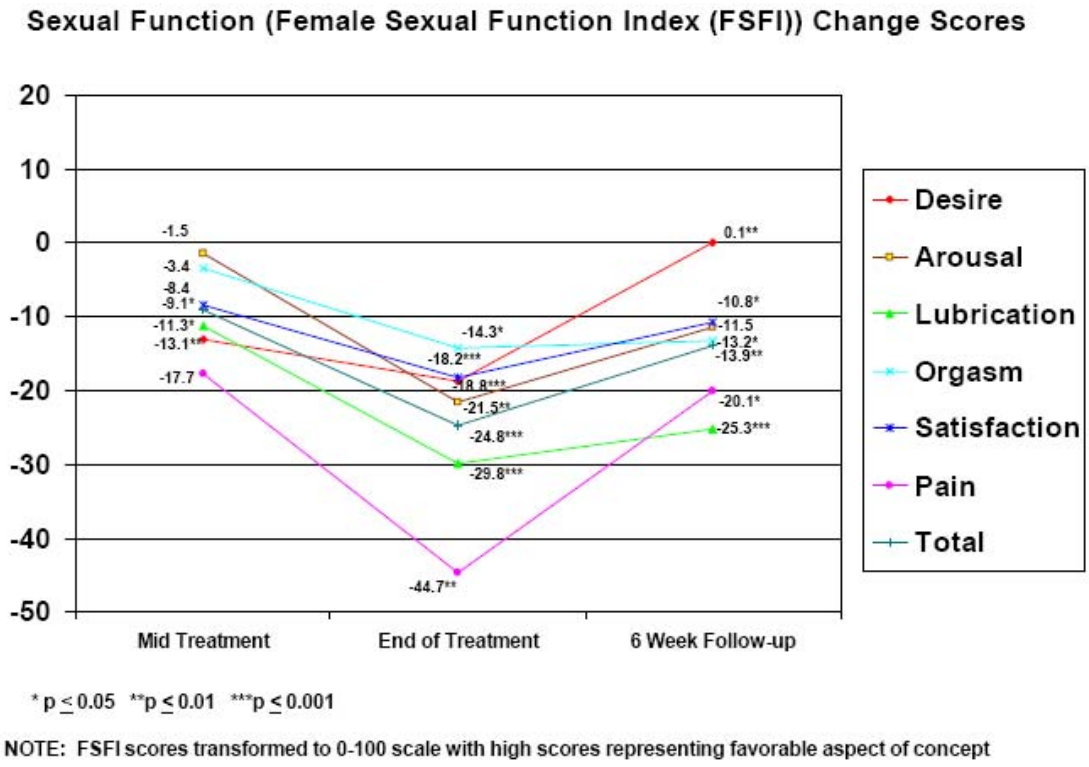
Vasomotor Symptoms (Green Climacteric Scale (GCS)) Change Scores



* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

NOTE: GCS scores transformed to 0-100 scale with high scores representing favorable aspect of concept

Appendix G: Sexual Function Change Scores



* p ≤ 0.05 **p ≤ 0.01 ***p ≤ 0.001

NOTE: FSFI scores transformed to 0-100 scale with high scores representing favorable aspect of concept

Appendix H: Difference in Change Scores Based on Age

Differences in Change Scores Based on Age

Androgens and Androgen Precursors								
	Baseline Median Scores		Mid-Treatment		End of Treatment		6 Month Follow-up	
	< 40	≥ 40	<40	≥40	<40	≥40	<40	≥40
Testosterone	3.6	2.1	-1.2	-0.5	-2.2	-0.7	-1.2	-0.5
Androstendione	123.0	89.0	-50.4	-27.7	-79.0**	-29.1**	-45.3	-31.9
DHEA-S	124.0	100.0	3.1	-10.6	-10.9	-6.7	-1.8	6.9
Sex Hormone Binding Globulin								
SHBG	45.0	58.0	16.0	4.2	19.7*	5.5*	23.9	15.6
Estrogens and Estrogen Precursors								
	Baseline Median Scores		Mid-Treatment		End of Treatment		6 Month Follow-up	
	< 40	≥ 40	<40	≥40	<40	≥40	<40	≥40
Estradiol	72.0	77.0	-5.4	-86.3	-33.7	-126.9	113.0**	-138.1**
Estrone	60.0	70.0	-25.6	-38.5	-38.6	-57.5	21.5	-58.6
FSH	4.0	8.0	10.0**	23.2**	45.8*	67.1*	37.0	64.8

NOTE: < 40 (N = 7) , ≥ 40 (N = 13)
*p ≤ .05
** p ≤ .01